REMARKS

The specification has been amended to reflect the national stage status.

In addition, claims 5 and 6 have been amended in accordance with the Amendment submitted during prosecution of the international application under Article 19.

Furthermore, the specification has been amended according to the amendments presented during prosecution of the International Application under Article 34, replacing pages 7, 8, 9, 19 and 27 with the attached replacement pages.

Favorable action on the merits is solicited.

Respectfully submitted,

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thrombus formation, or using a medicinal composition for improving the movement of the digestive tract comprising the ameliorant and a pharmaceutically acceptable carrier,

(4) a method for improving the movement of the digestive tract of a human or an animal, while avoiding occurrence of arteritis, thrombus formation or encephalomalacia, which comprises administering 4-amino-5-chloro-2-methoxy-N-[(2S, 4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide or an acid addition salt thereof, or a medicinal composition comprising the ameliorant and a pharmaceutically acceptable carrier to a human or a mammal,

(5) 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidynyl]benzamide or an acid addition salt thereof,

(6) 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide in which an amino group at position 4 or/and an amino group of the pyrrolidinyl group may be protected, or an acid addition salt thereof,

(7) a process for preparing 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide or an acid addition salt thereof, which comprises reacting 4-amino-5-chloro-2-methoxybenzoic acid having an optionally protected amino group or a reactive derivative thereof with (2S, 4S)-4-amino-N-acyl-2-hydroxymethylpyrrolidine to obtain 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-1-acyl-2-hydroxymethyl-4-pyrrolidinyl]benzamide or an acid addition salt thereof, and eliminating a protecting group and the acyl group, when a protecting group is used in the acyl group,

(8) (2S,4S)-4-amino-N-acyl-2-hydroxymethylpyrrolidine having an optionally protected amino group,

(9) the compound according to the above (8), wherein a protecting group for an amino group is an acyl group, and the acyl group and an acyl group of N-acyl are selected from formyl, acetyl, propionyl and benzoyl, and

(10) the compound according to the above (8), wherein the acyl group is acetyl.

The present invention will be explained in more detail below by describing embodiments, but they should not be construed as limiting the scope of this invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a change in binding affinity for a serotonin receptor 4, of a specimen drug. An abscissa axis indicates a concentration (molar concentration; logarithmic expression) of a specimen drug, and an ordinate axis indicates a ratio of binding of a serotonin receptor 4 and [^{3}H] GR113808. ●---● indicates a specimen compound obtained in Example 9, and ○---○indicates TKS159 hydrochloride. As a concentration of a specimen drug grows higher, an amount of [^{3}H]GR113808 bound to a serotonin receptor 4 is reduced. That is, it is indicated that a specimen drug binds to a serotonin receptor 4, antagonizing [^{3}H]GR113808 binding to the serotonin receptor 4. It is seen that affinity of a specimen drug obtained in Example 9 for a serotonin receptor 4 is stronger as compared with affinity of TKS159 hydrochloride.

Fig. 2 indicates a change in binding affinity for a dopamine D_2 receptor, of a specimen drug. An abscissa axis indicates a concentration (molar concentration; logarithmic expression) of a specimen drug, and an ordinate axis indicates a ratio of binding of a dopamine D_2 receptor and [^{3}H]-spiperone. ●---● indicates

a specimen compound obtained in Example 9, and ○---○ indicates TKS159 hydrochloride. As a concentration of a specimen drug grows higher, an amount of [^{3}H]-spiperone bound to a dopamine D_2 receptor is reduced. That is, it is indicated that a specimen drug binds to a dopamine D_2 receptor by antagonizing [^{3}H]-spiperone binding thereto. It is seen that affinity of a specimen drug obtained in Example 9 for a dopamine D_2 receptor is weaker as compared with affinity of TKS159 hydrochloride.

Fig. 3 indicates a degree of a relaxing reaction of a specimen drug in a rat-extracted specimen. An abscissa axis indicates a concentration (molar concentration; logarithm expression) of a specimen drug, and an ordinate axis indicates a ratio of relaxation in a rat-extracted specimen. ●---● indicates a specimen compound obtained in Example 9, and ○---○ indicates TKS159-hydrochloride. As a concentration of a specimen drug grows higher, relaxation of a specimen is caused in a concentration-dependent manner, and it is seen that action of a drug obtained in Example 9 is stronger as compared with TKS159 hydrochloride.

BEST MODE FOR CARRYING OUT THE INVENTION

4-Amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide of the present invention or an acid addition salt thereof can be prepared by reacting 4-amino-5-chloro-2-methoxybenzoic acid having an optionally protected amino group represented by the formula (I):

pyrrolidinyl]benzamide monohydrochloride on serotonin receptor 4:

Corpus striatum extracted from a Hartley male guinea pig was homogenized in a 50 mM HEPES-NaOH buffer (pH 7.4), and centrifugation and suspension were repeated to prepare a serotonin receptor 4 sample. The receptor sample was reacted with a solution containing a 0.1 nM radioactive ligand of [^{3}H]-GR113808 and the specimen drug obtained in Example 9 at a prescribed concentration. Then, the solution was filtered by suction using a multifilter MF-12G (glass filter (provided with Whatman GF/C)), and radioactivity of the filter was measured using a scintillation counter (LS6500 Beckman), so that affinity of the specimen drug for a serotonin receptor 4 was measured. Separately, the same procedure was also performed regarding TKS159 hydrochloride, and the affinity was compared.

The results are shown in Fig. 1. IC_{50} is 0.25 μM, which is a lower concentration than 0.45 μM of TKS159 hydrochloride.

[Example 2]

Measurement of action of 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide monohydrochloride on dopamine D_2 receptor:

Corpus striatum extracted from a Wistar male rat was homogenized in a 50 mM Tris-HCl buffer (pH 7.7), and centrifugation and suspension were repeated to prepare a dopamine D_2 receptor sample. The receptor sample was reacted with a solution containing a 0.25 nM radioactive ligand of [^{3}H]-spiperone and the specimen drug obtained in Example 9 at a prescribed concentration. Then, the solution was filtered

An esophagus in a chest cavity was extracted from a Wistar male rat, and muscularis propria sample containing longitudinal muscle and circular muscle was removed to prepare a muscularis mucosae sample having a length of about 2 cm. The sample was immersed in a nutrient solution (containing NaCl 118.5, KCl 4.7, $CaCl_2$ 1.3, $MgSO_4$ 0.6, $NaHCO_3$ 25.0, KH_2PO_4 1.2, and glucose 11.1 (unit mM)), and constriction of the sample and stability of the constriction were confirmed at 32°C using 3×10^{-6} M carbachol while a 95% O_2/5% CO_2 mixed gas was flown, each 1 μM of methysergide, ketanserin and granisetron were added, the drug obtained in Example 9 was accumulatively applied at a common ratio of 3 after 30 minutes, and a degree of relaxation was isotonically (stationary tension; about 0.5 g) measured via a transducer. Separately, the same procedure was also performed regarding TKS159 hydrochloride, and an intensity of the action was compared.

The results are shown in Fig. 3. EC_{50} was 0.7 μM, which is a lower concentration than 1.1 μM of TKS159 hydrochloride.

[Example 13]

Using a ddy male mouse, the drug obtained in Example 9 and TKS159 were suspended in 0.5% methylcellulose for oral administration, and were dissolved in a physiological saline for intravenous administration. This was administered by a forced oral administration method and an intravenous administration method using a probe, and acute toxicity was observed.